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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/766,948

Applicant(s)

GYBACK ET AL.

Examiner

Zachary C. Tucker

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 and 19-63 is/are pending in the application.
- 4a) Of the above claim(s) 14,15 and 19-28 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 12 and 13 is/are allowed.
- 6) ☒ Claim(s) 1-11 and 29-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

Response to Amendment

Amendments to claims 1, 2, 5-14 and 19 have been entered, claims 16-18 have been cancelled and thirty-five new claims, numbered 29-63 have been added, as requested by applicants in the correspondence filed 5 June 2006 (hereinafter "present amendment"), which is in reply to the Office action mailed 3 March 2006 (hereinafter "previous Office action"). The specification has also been amended at page 13, lines 6-27, as requested.

Requirement for Restriction

It is noted that in the remarks accompanying the present amendment, applicants' counsel requests that withdrawn claims 14, 15 and 19-28 be rejoined and the Restriction Requirement be withdrawn. Withdrawn claims drawn to processes for the preparation of the compound according to claim 1 or 2, methods of treatment comprising administering the same to a mammal, and a pharmaceutical composition comprising the same as active ingredient will indeed be rejoined with the elected invention, Group I, so long as the withdrawn claims are commensurate in scope with Group I claims, at such time that the elected Group is in condition for allowance. Claims of Group I, the elected Group, are *not* in condition for allowance, so conditions required for rejoinder have not been met. Applicants should note that Group IV, claims drawn to intermediate compounds employed in processes for preparing compounds of Group I are not commensurate in scope with the Group I, so Restriction Group IV (claims 26-28) will not be rejoined, even when the claims of Group I are in condition for allowance.

Improper Multiply Dependent Claims

In the previous Office action, claims 5-11 were objected to under 37 C.F.R. 1.75(c) for being in improper form. Multiply dependent claims cannot depend from other multiply dependent claims. In view of the present amendment to claims 5-11, the objection is hereby withdrawn.

Claims 5-11 will now be treated on the merits in this Office action.

Status of Claim Rejections - 35 USC § 112

In the previous Office action, claims 1-4, 12 and 13 were rejected under the first paragraph of 35 U.S.C. 112, for lack of a disclosure enabling the claimed solvates and solvates of the pharmaceutically acceptable salts of the compounds having the formula I. In view of the present amendment to claims 1, 2, 12 and 13, striking the language referring to these forms of formula I compounds, the rejection under the first paragraph of 35 U.S.C. 112, of claims 1-4, 12 and 13 is hereby withdrawn.

Indefinite language in claims 1, 2, 3 and 4 served as grounds for rejection of those claims under the second paragraph of 35 U.S.C. 112, in the previous Office action.

In view of the amendment to claim 1, converting "C₁₋₃alkyl" to "C₁₋₃alkylene" in the definition of X², the rejection for indefiniteness is withdrawn insofar as that variable was found to be indefinite.

In the definition for R² and R⁴ in claim 1, the term "C₀₋₃alkylhydroxy" was deemed indefinite, as the term is not a "term of art" so to speak. Applicants' traversal of this ground of rejection states that the meaning of this term is clear, because at page 7,

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lines 15-19 in the instant specification, it is set forth that when the subscript is zero, then whichever group being described thusly is absent. The examiner was aware of the cited passage in the instant specification when the previous Office action was prepared. It was not averred in the Office action that the meaning of the term "C₀₋₃alkylhydroxy" is not understood when the subscript on "alkyl" is zero, rather the rejection was made on grounds that the term is indefinite when the subscript is *not* zero. What exactly constitutes an "alkylhydroxy" group is not defined in the specification. Does this term refer to an alkyl group substituted with a hydroxy group, or does it contemplate an alkoxy group? If the latter is the case, then ambiguity is introduced by virtue of the fact that other recitations of alkoxy are present in the definition for variable R⁴. How the "C₁-alkylhydroxy" group differs from "methoxy," for instance, is not understood. It would seem that if applicants intended "alkoxy" by "alkylhydroxy," then the art accepted terminology "alkoxy" would be more logical and appropriate, especially since "alkoxy" is recited elsewhere in the claims and specification. In any case, the specification does not define "alkylhydroxy" to any extent, it only speaks to the significance of a zero subscript, in general, and not specifically with respect to "alkylhydroxy," or any specific term recited in the claims.

Similarly, the term "C₀₋₃alkyldimethylamino" was deemed indefinite. Applicants' traversal of this ground of rejection is the same as was stated for the rejection based on indefiniteness of the term "C₀₋₃alkylhydroxy" – that it is clearly defined because the specification teaches that when the subscript is zero, then the thusly-described group is absent. On the contrary, however, in the case of the term "C₀₋₃alkyldimethylamino" it is not completely clear what functional group is embraced with the subscript is zero. Does

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the term contemplate simply a dimethylamino group when the subscript is zero, or does the zero subscript necessitate that no alkyl group is on the amino function, which would provide for an unsubstituted amino group? The passage from the specification, cited by applicants' counsel, would tend to suggest that the zero subscript, in the case of "C₀₋₃alkyldimethylamino," provides for an amino group with no alkyl groups bonded thereto.

What is further unclear about "C₀₋₃alkyldimethylamino" is what applicants intend for the term to embrace when the subscript is *not* zero. For instance, is the extra alkyl group on the dimethylamino group bonded to the *nitrogen atom*, which would afford a positively charged quaternary ammonium function, or is the extra alkyl group bonded to one of the methyl groups already present on the dimethylamino group, providing for a dialkylamino group with one alkyl group larger than methyl? The difference is important, as a quaternary ammonium group, an unsubstituted amino group and dialkylamino groups are quite different chemically.

The specification does not satisfactorily define either "C₀₋₃alkylhydroxy" or "C₀₋₃alkyldimethylamino." Merely stating –

In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to indicates that the group is absent.

says nothing about what is intended when the subscript is a non-zero number, in the instance of the two terms criticized hereinabove, and further does not make clear what is intended by "C₀alkyldimethylamino." The rejection is maintained.

In the definition of R³ in claim 2, the term "C₀₋₃alkylOC₂₋₄alkanol C₁₋₃alkanol" was found to be indefinite. In view of the amendment to claim 2, inserting a comma between

"C₀₋₃alkylOC₂₋₄alkanol" and "C₁₋₃alkanol," that ground of rejection under the second paragraph of 35 U.S.C. 112 is hereby withdrawn.

However, the term "alkanol" appears as one of the alternatives specified in the definition of R³ in claims 1 and 2. An "alkanol" refers to an alcohol, which is a compound unto itself, not a substituent on a molecule. Applicants' traversal of this ground of rejection under 35 U.S.C. 112, second paragraph points to page 8, lines 9-12 of the specification. Contrary to what applicants' counsel states, this passage *does not* set forth the definition of "alkanol" as "an alkyl group which contains a hydroxyl group." Nowhere in the specification is such a statement found.

Page 8, lines 9-12 of the instant specification read as follows:

In this specification, unless stated otherwise, the term "alkanol" includes both straight and branched chain alkanol groups. The term C₁₋₃alkanol having 1 to 3 carbon atoms and one hydroxy group may be, but is not limited to methanol, ethanol or propanol and a propanol group may for example be 1-propanol or 2-propanol.

The cited passage speaks generally of alcohols, which, as was indicated in the previous Office action, are not substituent groups on a molecule, rather an alcohol is a discrete compound in and of itself.

The ground of rejection under 35 U.S.C. 112, second paragraph, wherein the term "alkanol" as alternative identity of R³ is deemed to be indefinite is maintained.

Status of Claim Rejections - 35 USC § 102

In the previous Office action, claims 1-3 were rejected under 35 U.S.C. 102(b) as being anticipated by Keir and MacLennan, *Journal of the Chemical Society, Perkin Transactions 1*, vol. 9, pages 1002-1006 (1978).

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The compound 3-amino-5,6,7,8-tetrahydrobenzo[b]pyrazine-2-(N-cyclohexyl)carboxamide is disclosed in the reference, which is embraced by instant claims 1-3 wherein Q is a six-membered saturated cycloalkyl ring (cyclohexyl fused to pyrazine); P is a six-membered fully saturated cycloalkyl ring (cyclohexyl); m and n are both equal to zero; X¹ is oxygen; X² is a bond; R² is hydrogen; R⁴ is amino (-NH₂), or "C₀alkylamino" as recited in the definition of R⁴ in claim 1.

Claim 2 was included in the rejection based on Keir and MacLennen in error, as R⁴ is required to be hydrogen in claim 2, while the reference compound corresponds to R⁴=amino.

In view of the present amendment to claim 1, the rejection based on Keir and MacLennen is hereby withdrawn. The compound disclosed by Keir and MacLennen is no longer embraced by instant claim 1, because a new exclusionary proviso reciting that compound has been added by virtue of the present amendment.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

This new rejection under the first paragraph of 35 U.S.C. 112, is made necessary by the present amendment.

Claims 1, 3-11 and 29-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The new proviso in claim 1, specifically excluding the compound 3-amino-5,6,7,8-tetrahydrobenzo[b]pyrazine-2-(N-cyclohexyl)carboxamide, is new matter. Applicants' counsel does not point to where in the specification support for this proviso is found. Indeed, the proviso was not in the claims or specification as originally filed. In the remarks accompanying the present amendment, applicants' counsel states that the amendment is appropriate, since formula I encompasses this compound as a species within a recited genus. Applicants' counsel states that is permissible to disclaim a portion of a recited genus, citing MPEP 2173.05(i).

The new proviso is new matter because the variables of formula I, as are set forth in the claims and specification as was originally presented, are independent of one another. The new proviso, however, creates a new relationship between those variables that was not described in the specification and claims before. There are no teachings in the disclosure that would lead one of ordinary skill to determine that applicants' invention was intended to include or exclude this one particular compound from the genus of formula I, out of the millions which are embraced by formula I. In fact, the MPEP citation offered by applicants' counsel as justification for the new proviso specifically instructs the examiner to *reject* provisos such as the one at hand on grounds that they are new matter.

The second paragraph in MPEP 2173.05(i), the chapter cited by applicants' counsel, reads as follows:

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) (“[the] specification, having described the whole, necessarily described the part remaining.”). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff’d mem.*, 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993).

In light of this passage, it could not be more clear that the proviso in claim 1 as presently amended constitutes new matter. It would seem that the case law cited by applicants’ counsel has therefore been misunderstood. The decisions from the two cited cases (referred to in the excerpt from MPEP, *supra*, and remarks by applicants’ counsel) determined that if a negative limitation in the claims excludes an embodiment of the invention which is *positively recited* in the disclosure, then that negative limitation is acceptable. Nowhere, however, in the instant specification or claims is the compound excluded by the newly added proviso recited, so its exclusion from formula I clearly constitutes new matter. In other words, if the compound excluded by the newly added proviso were recited in the claims or specification as originally filed, then the proviso would not be considered new matter.

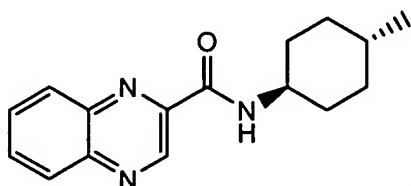
Upon review of instant claim 2, specifically with respect to the definition of ring “Q,” the following rejection is seen as necessary.

New Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2-11 and 29-63 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/26927 (Van Wagenen et al).

Van Wagenen et al describes the synthesis of the compound N-(*trans*-4-methylcyclohexyl)-2-quinoxalincarboxamide on page 26, which compound has this structure:



and is a compound according to instant claims 2-11 and 29-63 wherein R¹ is methyl, m=1; R² is hydrogen; X¹ is oxygen; X² is a bond; R³ is hydrogen and n=1 – or n=0 and R³ is as defined in claim 2. R¹ and X² are *trans* orientation with respect to one another. The ring “Q” in the compound from Van Wagenen et al is a ring containing 6 carbon atoms. The definition of “Q” in claim 2 does not require the ring to be either saturated or partially unsaturated, it merely states that the ring “Q” is *permitted to be* saturated or partially unsaturated.

Allowable Subject Matter

Claims 12 and 13 are allowed; there is no disclosure of, nor any suggestion rendering obvious any of the compounds specified in claims 12 and 13.

The rejection under 35 U.S.C. 102(b), based on Keir and MacLennen will be properly overcome, without introducing new matter, by an amendment to claim 1 deleting “C₀₋₃alkylamino” and “C₀₋₃alkyldimethylamino” from the Markush group in the definition of variable R⁴ in claim 1.

Deletion of "alkanol" in all occurrences and forms, deletion of "C₀₋₃alkyldimethylamino" and deletion of "C₀₋₃alkylhydroxy" would overcome the indefiniteness rejections under the second paragraph of 35 U.S.C. 112.

Amendment of claim 2 along the lines of the present amendment to "Q" of claim 1 - "Q is a saturated or partially unsaturated ring containing 4, 5, 6 or 7 atoms independent selected from C, S, O and N" (and deleting the recitation of "which may be saturated or partially unsaturated") would overcome the new rejection under 35 U.S.C. 102(b) set forth hereinabove.

It is recommended that applicants review the reference submitted with the Requirement for Restriction letter, authored by Ritzén et al, and amend the method-of-use claims accordingly. Treatment of schizophrenia, epilepsy and pain are enabled, as the reference characterizes those conditions as the most likely candidates for the actual therapeutic application of metabotropic glutamate receptor antagonists. Ritzén et al teaches that the treatment of Alzheimer's disease, Parkinson's disease, epilepsy and depression with metabotropic glutamate receptor antagonists is theoretical and not completely understood.

Instant claims 19 and 24 are both too broad to be enabled by the disclosure and are indefinite, as the full scope of all "mGluR mediated disorders" was not known at the time the invention was made, and "inhibiting the activation of mGluR" is a claim drawn to the treatment of disorders resulting from too much mGluR activation and also too little, which could only be *worsened* by the compounds of the present invention. It is also noted that claim 24 recites redundant language, in that the abbreviation "mGluR"

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stands for "metabotropic glutamate receptor," while the word "receptor" is recited after "mGluR."

In addition to the citations of close prior art which were provided in the previous Office action (at pages 8-10), the examiner would in addition cite the following documents:

Kikuchi et al, "Syntheses and Structure - Activity Relationships of 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxaline Derivatives with Retinoic Acid Receptor α Agonistic Activity" *Journal of Medicinal Chemistry*, vol. 43, pages 409-419 (2000).

and

Jones et al, "Synthesis and Structure - Activity Relationships of 2-Pyrazinylcarboxamidobenzoates and β -lonylideneacetamidobenzoates with Retinoidal Activity" *Journal of Medicinal Chemistry*, vol. 41, pages 3062-3077 (1998).

Both of which disclose retinoid receptor agonists based on a 5,6,7,8-tetrahydroquinoxaline-2-carboxamide core structure. The ring corresponding to "P" of formula I of the instant claims is completely unsaturated, however.

Conclusion

This Office action is made non-final due to the new rejections under 35 U.S.C. 102, which were not made necessary by applicants' amendment.

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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